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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KUBELIK, ANNE R	

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1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,918	LELIVELT ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,43-66,82-84 and 86-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *53* is/are allowed.

6)☒ Claim(s) *41,43-52,54-66,82-84 and 86-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 41, 43-66, 82-84 and 86-92 are pending.

2. The objection to claims 43, 54-55 and 58-63 because informalities is withdrawn in light of Applicant's amendment of the claims.

3. The objection to claim 65 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in light of Applicant's cancellation of the claim.

4. The objection to claim 56 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in light of Applicant's amendment of the claim.

5. The rejection of claim 56 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in light of Applicant's amendment of the claim.

6. The rejection of claims 41, 43, 45-52 54-66 and 91-92 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of Asteraceae transformation where the transformation vector comprises a selection marker, does not reasonably provide enablement for a method of Asteraceae transformation where the transformation vector does not comprise a selection marker is withdrawn in light of Applicant's amendment of claim 41 to recite a selection marker.

Claim Objections

7. Claim 88 is objected to because of the following informalities: It lacks an article at the start of the claim.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 41, 43-52, 54-66, 82-84 and 86-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection, made because of Applicant's amendment of the claims, is different from the rejection set forth in the Office action mailed 19 June 2008, as applied to claims 43, 45, 47-52, 54-56, 86 and 88. Applicant's arguments filed 18 December 2008 have been fully considered but they do not apply to these new rejections.

Claim 41 is indefinite in its recitation of "with a liquid adding a selection agent to the culture medium comprising the plant material"; words appear to be missing from the claim, or words are out of order.

Claim 45 is indefinite in its recitation of "transformants carry the DNA of interest in the genome of the transformant". It is not clear that "transformant" has any relationship to the "transformants", and it appears words are missing from the claim. Further, which genome is being referred to here - plastid? Nuclear? Mitochondrial?

In claim 47, it is not clear what the promoter has to do with the rest of the method. Is it part of the expression vector? Is selecting it just something the practitioner does at some random point in the method?

Similarly, in claims 48-49, it is not clear what "a DNA of interest" has to do with the rest of the method.

Similarly, in claims 54-56, it is not clear what the DNA segments have to do with the rest of the method.

Similarly, in claim 86, it is not clear what the gene of interest has to do with the rest of the method.

Claim Rejections - 35 USC § 103

10. Claims 41, 43-47, 51, 54, 57-60, 64-66, 82-83, 86-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koop et al (1996, Planta 199:193-201). Due to Applicant's amendment of the claims, the rejection is modified from the rejection set forth in the Office action mailed 19 June 2008. Applicant's arguments filed 18 December 2008 have been fully considered but they are not persuasive.

The claims are drawn to a method of Asteraceae chloroplast transformation by PEG-mediated transformation of protoplasts.

Koop et al teach a method of tobacco leaf chloroplast transformation by PEG-mediated transformation of protoplasts (pg 194, left column, paragraph 4, to pg 195, left column, paragraph 2). In this method, a vector comprising an expression cassette comprising the Prrn promoter and rbcL ribosome binding site operably linked to the aadA selection marker operably linked to a termination sequence, flanked by the tobacco ndhF and trnL sequences as targeting segments that allow double homologous recombination (See Fig 1b), is transformed into tobacco protoplasts by PEG-mediated transformation. The protoplasts were embedded in alginate, then

placed in contact with a liquid medium that did not contain a selection agent (pg 195, left column, paragraph 1). After two weeks, they were transferred to solid selection medium containing spectinomycin and/or streptomycin (pg 195, left column, paragraph 1-2) and transformed plants and progeny produced.

Koop et al do not disclose a method of PEG-mediated Asteraceae plastid transformation, including transformation of lettuce with a vector containing lettuce sequences, the presence of a DNA insertion site for a sequence of interest, and a time of contact in the culture medium without a selection agent as short as two days or in the dark.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of plastid transformation as taught by Koop et al to apply the method to other plant species, including Asteraceae like lettuce. One of ordinary skill in the art would have been motivated to do so because Koop et al indicate that the method would be useful for a wide range of plant species (pg 201, left column paragraph 2), and because of the economic importance of such species.

At the time the invention was made, it would also have been obvious to one of ordinary skill in the art to modify the method of plastid transformation as taught by Koop et al to replace the tobacco flanking regions with the corresponding ones from the Asteraceae plastid one wishes to transform, including that of lettuce. One of ordinary skill in the art would have been motivated to do so because plastid transformation works by homologous recombination (Koop et al, pg 193, right column), and one of skill in the art would know that the higher the homology between the targeting segment and the target, the higher the probability of transformation.

One of ordinary skill in the art would have been motivated to include a DNA insertion site for receiving a DNA of interest sot that one could clone genes encoding proteins of interest into plastids. Additionally, it would be obvious to one of skill in the art to experiment with different lengths of times of exposure to the medium lacking a selection agent, and would have tried shorter times, including for only two days, in the optimization of experimental protocols. One of ordinary skill in the art would have placed the treated plant material in contact in the liquid culture medium without a selection agent in the dark in the optimization of experimental parameters, and it is one of only two available options. It also would be obvious to one of skill in the art to add the selection agent to the liquid culture medium, given that Koop et al suggested that lower transformation freq2euncy was due to poor contact of the cells with the solid selection medium (pg 200, left column, paragraph 1).

Applicant urges that Koop et al says that the applicability of each transformation method for different species will have to be determined in the future, recognizing that different species require different protocols; thus, it is not obvious to modify for lettuce the tobacco method of Koop et al (response pg 4).

This is not found persuasive because Kop et al suggest modifying the protocol for each species; Koop et al do not say it would not work in Asteraceae.

Applicant urges that there are critical differences between Koop's method and the instant method; Applicant's method requires selection at a relatively early stage, preferably 2-5 days or after 6 days, and Applicant's method does not use fresh culture medium for the initial selection (response pg 4).

This is not found persuasive. It would be obvious to one of skill in the art to experiment with different lengths of times of exposure to the medium lacking a selection agent, and would have tried shorter times, including for only two days, in the optimization of experimental protocols. It also would be obvious to one of skill in the art to add the selection agent to the liquid culture medium, given that Koop et al suggested that a lower transformation frequency was due to poor contact of the cells with the solid selection medium (pg 200, left column, paragraph 1).

11. Claims 49-50, 55-56 and 61-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koop et al (1996, Planta 199:193-201) as applied to claim s 41, 43-47, 51, 54, 57-60, 64-66, 82-83, 86-89 above, and further in view of Blowers et al (WO 99/05265). The rejection is repeated for the reasons of record as set forth in the Office action mailed 19 June 2008. Applicant's arguments filed 18 December 2008 have been fully considered but they are not persuasive.

The claims are drawn to a method of lettuce plastid transformation, using the psbA terminator, use of lettuce 70B /trnV/16S/trnI/trnA as flanking sequences, and particle bombardment as the transformation method.

The teachings of Koop et al are discussed above. Koop et al do not teach the psbA terminator, use of lettuce 70B /trnV/16S/trnI/trnA as flanking sequences, sequences of interest providing herbicide resistance, and use of particle bombardment as the transformation method.

Blowers et al teach transformation of tobacco plastid genomes by transforming by particle gun transformation nonphotosynthetic tobacco suspension cells with a plasmid comprising an expression cassette comprising the Prrn promoter operably linked to distronic

gusA-aadA or hph-aadA or tricistronic glpB-hph-aadA operably linked to the psbA terminator and flanked on one side by petunia 70B and the other by trnV/16S/trnI/trnA (Fig 3; pg 51, lines 1-9), placing the plant material for two days on medium lacking a selection agent, then transferring to medium comprising the selection agent spectinomycin or glyphosate, and maintaining the resulting calli on either solid or liquid selection media, thus, refreshing the culture medium comprising the selection agent (pg 42, line 20, to pg 44, line 22; pg 49, line 6, to pg 53, line 24; pg 54, line 1, to pg 57, line 10). The resulting transformed calli had the expression cassette inserted into the plastid genome (pg 47, lines 1-9).

The expression cassette comprises a HindIII insertion site (pg 43, lines 5-8), and the gusA coding sequence would be the gene of interest. The nonphotosynthetic tobacco suspension cells contain proplastids (pg 7, lines 2-5). GusA is a visual selection marker when the cells are grown in the correct medium. hph and glpB are genes of interest that confer resistance to the herbicide glyphosate. rps7/rsp12 and the other by trnI/trnA allow double homologs recombination of the DNA of interest with the plastid genome because they have a DNA sequence that is homologous to the a part of the plastid genome. As plant parts include calli and as transformed plastid containing cells were produced from those calli (pg 51, lines 16-19), progeny were produced from the plant parts.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of lettuce plastid transformation taught by Koop et al, to use the psbA terminator, use of lettuce 70B /trnV/16S/trnI/trnA as flanking sequences, sequences of interest providing herbicide resistance, and particle bombardment as the transformation method as described in Blowers et al. One of ordinary skill in the art would have been motivated to use

the psbA terminator and particle bombardment as the transformation method because selection of terminator and transformation method from those commonly used in the art is an obvious design choice. One of ordinary skill in the art would have been motivated to sequences of interest providing herbicide resistance because of agricultural practices that involve spraying herbicides on fields in which crop plants are growing.

One of ordinary skill in the art would have been motivated to use lettuce 70B/trnV/16S/trnI/trnA as flanking sequences because this region is commonly used in plastid transformation of other plant species. The exact breakpoint would be one of personal choice, and one of skill in the art would reasonably choose the breakpoint such that one flanking region comprises the trnI/trnA and the other 70B/trnV/16S. SEQ ID NOs:6-9 and/or 13-16 would thus be comprised within these sequences.

Applicant urges that Blowers et al teach transformation of Solanaceae plastids, not Asteraceae plastids (response pg 5).

This is not found persuasive because Koop et al makes obvious transformation of Asteraceae plastids, as discussed above.

Applicant urges that Blowers et al teach using a solid medium (response pg 5).

This is not found persuasive because Koop et al makes obvious use of a liquid medium, as discussed above.

12. Claims 48 and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koop et al (1996, Planta 199:193-201) as applied to claim s 41, 43-47, 51, 54, 57-60, 64-66, 82-83, 86-89 above, and further in view of Daniell (WO 99/10513). The rejection is repeated for the reasons

of record as set forth in the Office action mailed 19 June 2008. Applicant's arguments filed 18 December 2008 have been fully considered but they are not persuasive.

The claims are drawn to a method of transforming Asteraceae with a DNA of interest encoding a therapeutic or prophylactic (bio)pharmaceutical (poly)peptide.

The teachings of Koop et al are discussed above. Koop et al do not teach the DNA of interest encoding a therapeutic or prophylactic (bio)pharmaceutical (poly)peptide.

Daniell et al suggests expression of therapeutic or prophylactic (bio)pharmaceutical (poly)peptides, including edible vaccines, in plant plastids (pg 14, lines 13-22; pg 31, line 9, to pg 33, line 19).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of transforming Asteraceae as taught by Koop et al to express a DNA encoding a therapeutic or prophylactic (bio)pharmaceutical (poly)peptide as described in Daniell et al. One of ordinary skill in the art would have been motivated to do so because of the suggestion of Daniell to express these proteins in plastids (pg 14, lines 13-22; pg 31, line 9, to pg 33, line 19).

Applicant urges that Daniell does not teach using liquid medium (response pg 5).

This is not found persuasive because Koop et al makes obvious use of a liquid medium, as discussed above.

13. Claim 53 is free of the prior art, given the failure of the prior art to teach or suggest a method of plastid transformation comprising culturing the transformed plastids of Asteraceae on media lacking a selection agent before selecting transformants with a light source corresponding

to a visual marker. Claims 52 and 91-92 are free of the prior art given the failure of the prior art to teach or suggest a method of plastid transformation using a visual marker as a selection agent.

14. Claims 51 and 91-92 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

15. Claim 53 is allowed.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, Ph.D., whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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April 16, 2009

/Anne R. Kubelik/
Primary Examiner, Art Unit 1638